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SALIWANCHIK LLOYD & SALIWANCHIK A PROFESSIONAL ASSOCIATION 2421 N.W. 41ST STREET			EXAMINER	
			WILSON, MICHAEL C	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No. 09/760,274

Applicant(s)

Examiner

Art Unit

Sinden et al.

Michael C. Wilson 1632

The MAILING DATE of this communication appears on the cover sheet with the correspondence address					
Period for Reply A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE3 MONTH(S) FROM					
THE MAILING DATE OF THIS COMMUNICATION.					
- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the					
- If the pe	mailing date of this communication If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.				
	eriod for reply is specified above, the maximum statutory period will apply at o reply within the set or extended period for reply will, by statute, cause th	nd will expire SIX (6) MONTHS from the mailing date of this communication. e application to become ABANDONED (35 U.S.C. § 133).			
	ly received by the Office later than three months after the mailing date of the patent term adjustment. See 37 CFR 1.704(b).	is communication, even if timely filed, may reduce any			
Status	ration tolin adjustment. Good of GTN 1.704(b).				
	Responsive to communication(s) filed on Oct 7, 200	02			
	This action is FINAL . 2b}□ This acti				
	3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is				
closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.					
Dispositi	on of Claims				
4) 🗶	Claim(s) <u>57-67</u>	is/are pending in the application.			
48	a) Of the above, claim(s)	is/are withdrawn from consideration.			
5) 🗌	Claim(s)	is/are allowed.			
6) 💢	Claim(s) <u>57-67</u>	is/are rejected.			
7) 🗆	Claim(s)	is/are objected to.			
8) 🗌	Claims	are subject to restriction and/or election requirement.			
Application Papers					
9) The specification is objected to by the Examiner.					
10)	The drawing(s) filed on is/are	a) accepted or b) objected to by the Examiner.			
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).					
11)		is: a) approved b) disapproved by the Examiner.			
If approved, corrected drawings are required in reply to this Office action.					
12) The oath or declaration is objected to by the Examiner.					
Priority under 35 U.S.C. §§ 119 and 120					
13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).					
a) □ All b) □ Some* c) □ None of:					
1. Certified copies of the priority documents have been received.					
	2. Certified copies of the priority documents have				
	B. Copies of the certified copies of the priority do	· · · · · · · · · · · · · · · · · · ·			
application from the International Bureau (PCT Rule 17.2(a)). *See the attached detailed Office action for a list of the certified copies not received.					
14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).					
a) The translation of the foreign language provisional application has been received.					
15) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.					
Attachment(s)					
_	ice of References Cited (PTO-892)	4) Interview Summary (PTO-413) Paper No(s).			
2) Noti	ice of Draftsperson's Patent Drawing Review (PTO-948)	5) Notice of Informal Patent Application (PTO-152)			
3) 🗌 Info	rmation Disclosure Statement(s) (PTO-1449) Paper No(s).	6) Other:			

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DETAILED ACTION

Election/Restriction

This application contains claims 1-48 drawn to an invention nonelected with traverse in Paper No. 8. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's arguments filed 10-7-02, paper number 10, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 49-56 have been canceled. Claims 57-67 have been added and are under consideration in the instant office action.

Specification

The first line of the specification needs updated to reflect the status of parent application 09/043,061 as abandoned.

Priority

Claims 57-67 have support in the instant application, parent application 09/672606 and parent application 09/043061 (all of which have the same disclosure). The specification teaches isolating cells from the hippocampus of embryonic day 14, H-2Kb-tsA58 transgenic mice. All cells of the mice are conditionally immortal because they are genetically modified to have a temperature-sensitive oncogene (tsA58) (pg 9, lines 1-15). MHP36 are a clonal cell line "derived" from H-2Kb-tsA58 hippocampal cells (Example 6, pg 24, last 12 lines). The specification teaches MHP15 and MHP36 cells are nestin positive on pg 20, Example 4. The

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specification teaches administering MHP36 intracerebrally in Example 6, pg 24, and administering MHP15 intracerebrally in Example 8, pg 27. The cells were cultured in permissive conditions (immortal), removed from permissive conditions (non-permissive, allows differentiation) and grafted into rats (para. bridging pg 24-25). The rats are a model for cognitive deficit (pg 25, first para.; para. bridging pg 9-10). Therefore, the claims have support in the instant application, parent application 09/672606 and parent application 09/043061 which all have the same disclosure.

The priority document cannot be found in 09/672606.

Claim Rejections - 35 USC § 112

1. The rejection of claims 49-56 under written description is withdrawn because the claims have been canceled and because claims 57-67, drawn to a similar invention, has support in the specification as originally filed. The specification teaches isolating cells from the hippocampus of embryonic day 14, H-2Kb-tsA58 transgenic mice. All cells of the mice are conditionally immortal because they are genetically modified to have a temperature-sensitive oncogene (tsA58) (pg 9, lines 1-15). MHP36 are a clonal cell line "derived" from H-2Kb-tsA58 hippocampal cells (Example 6, pg 24, last 12 lines). The specification teaches MHP15 and MHP36 cells are nestin positive on pg 20, Example 4. The specification teaches administering MHP36 intracerebrally in Example 6, pg 24, and administering MHP15 intracerebrally in Example 8, pg 27. The cells were cultured in permissive conditions (immortal), removed from permissive conditions (non-

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permissive, allows differentiation) and grafted into rats (para. bridging pg 24-25). The rats are a model for cognitive deficit (pg 25, first para.; para. bridging pg 9-10). Therefore, the claims have support in the instant application, parent application 09/672606 and parent application 09/043061 which all have the same disclosure.

20, example 4, does not support differentiating cells into neurons or glial cells *in vivo*. The example is directed toward *in vitro*.

2. Claims 57-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for implanting rat hippocampal neuroepithelial cells in the hippocampus of a rat having a damaged hippocampus, does not reasonably provide enablement for using any conditionally immortal cell, or implanting the cells anywhere intracerebrally as broadly claimed to improve a cognitive disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

The state of the art at the time of filing was such that it is unpredictable how to target particular areas of the brain when transplanting neural cells (Scheffler 1999, Trends in Neurosci, Vol. 22, pg 348-357; see para. bridging pg 354-355). The specification teaches obtaining H-2Kb-tsA58, hippocampal, pluripotent neuroepithelial cells, culturing the cells in "permissive" conditions (immortal), removing the cells from "permissive" conditions (cells begin to differentiate) and transplanting the cells to the CA1 area of rats with damaged CA1 tissue. The rats receiving H-2kb-tsA58 cells showed improved performance as compared to the ischemia

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control animal and an equivalent performance as compared to a sham control animal in the water maze test (Example 5, pg 22; pg 23, line 8; Fig. 9). The specification also teaches obtaining MHP36, a clonal cell line derived from the H-2Kb-tsA58, hippocampal neuroepithelial cells, which showed similar results (Example 6, pg 24, Fig. 10). The MHP36 cell line is nestin-positive as claimed (Example 4, pg 21, lines 1-6).

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The hippocampal lesion/water maze model used by applicants is an assay for cognitive disfunction (para. bridging pg 9-10). Sinden (1997, Neuroscience, Vol. 81, pages 599-608) teach that for transplanted neural cells to restore performance in water maze tests, the cells must be CA1 cells derived from the hippocampus and highly specific to the damaged CA1 tissue (page 601, paragraph bridging columns 1 and 2). For example, CA1 cells are effective, but CA3 cells derived from the hippocampus or cells derived from other portions of the brain are not effective (page 601, sentence bridging columns 1 and 2).

The specification does not enable using any "pluripotent, nestin-positive, neuroepithelial cells" to treat any lesion causing "cognitive deficit" (claim 57) other than hippocampal, pluripotent, neuroepithelial cells expressing nestin injected into a hippocampal lesion. The specification does not correlate the hippocampal, pluripotent, nestin-positive, neuroepithelial cells (H-2kb-tsA58 or MHP36) to any other "pluripotent, nestin-positive, neuroepithelial cells" such that cells having a similar structure as those found in the hippocampus or a similar therapeutic effect to a lesion in the hippocampus could be obtained. The specification does not teach any cells that can restore function to the hippocampus other than hippocampal cells. The

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permissive, allows differentiation) and grafted into rats (para. bridging pg 24-25). The rats are a model for cognitive deficit (pg 25, first para.; para. bridging pg 9-10). Therefore, the claims have support in the instant application, parent application 09/672606 and parent application 09/043061 which all have the same disclosure.

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Page 20, example 4, does not support differentiating cells into neurons or glial cells in vivo. The example is directed toward in vitro. Therefore, claim 59 is new matter.

2. Claims 57-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for implanting rat hippocampal neuroepithelial cells in the hippocampus of a rat having a damaged hippocampus, does not reasonably provide enablement for using any conditionally immortal cell, or implanting the cells anywhere intracerebrally as broadly claimed to improve a cognitive disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

The state of the art at the time of filing was such that it is unpredictable how to target particular areas of the brain when transplanting neural cells (Scheffler 1999, Trends in Neurosci, Vol. 22, pg 348-357; see para. bridging pg 354-355). The specification teaches obtaining H-2Kb-tsA58, hippocampal, pluripotent neuroepithelial cells, culturing the cells in "permissive" conditions (immortal), removing the cells from "permissive" conditions (cells begin to differentiate) and transplanting the cells to the CA1 area of rats with damaged CA1 tissue. The rats receiving H-2kb-tsA58 cells showed improved performance as compared to the ischemia

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should be limited to treating lesion in the hippocampus, using "hippocampal, pluripotent, neuroepithelial cells expressing nestin," and injecting the cells into the hippocampus.

The specification does not enable using any cells that are "genetically modified to be conditionally immortal" (claim 57) as broadly claimed. The transgenic mouse from which the "conditionally immortalized" cells disclosed in the specification originated (H-2Kb-tsA58) were known in the art (para. bridging pg 8-9). However, the structure and function of those cells is essential to the instant invention. For the cells to be immortal prior to administration and differentiate after administration as claimed, the cells must have the temperature sensitive oncogene tsA58 constructs which is the only oncogene disclosed or known in the art that has such a capability.

The rejection regarding the breadth of "animal" has been withdrawn because the claims have been amended to "mammal" and because the rats having a lesion in the hippocampus used throughout the specification were treated with mouse cells.

Applicants argue and the Declaration by Dr. Sinden states there was no selection of nestin-positive, pluripotent cells prior to applicants work. The instant application does not teach selecting cells from a mixed population of embryonic neural cells based on their expression of nestin. The specification merely teaches cloning a population of pluripotent neuroepithelial cells and determining that the clonal cell line expressed nestin. Furthermore, nestin-positive, pluripotent cell lines were known in the art at the time of filing to differentiate into multiple

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phenotypes (Renfranz, 1991, Cell, Vol. 66, pg 713-729). How this argument relates to treating a site of damage by administering the cells anywhere intracerebrally is unclear.

Applicants argue the cells of the invention inherently migrate to the sit of damaged tissue (also pg 5, 2nd para., last sentence, of specification). Applicants argument is not persuasive. Applicants have not provided adequate guidance to overcome the unpredictability in treating neural disease using pluripotent neural cells such that a therapeutic effect is obtained. While the cells of the invention may migrate to damaged tissue, applicants have not provided adequate guidance indicating the number of cells that migrate to the damaged tissue are adequate to improve cognitive function as claimed. Proof that the cells migrate upon being transplanted (para. 5 of declaration) is not adequate prove that the cells preferentially move to the site of damage, or that adequate numbers of cells move to the site of damage to improve cognitive function. The specification does not teach the number of cells that must move to the site of damage to improve cognitive function or that adequate numbers of cells can move to the site of damage to improve cognitive function. Application 09/537617 does not provide adequate evidence because the rats received 8 injections intracerebrally including at least one into the site of damage (pg 2, para. 0032; pg 3, para. 0034). Applicants have provided no evidence that cells injected intracerebrally into a remote site improves cognitive function. Without such guidance, the specification does not enable injecting the cells to any site intracerebrally as broadly claimed for reasons of record.

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3. Claims 57-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

The rejections regarding "permissive conditions" (49), "into the damaged brain of said animal" (49), "mammal which comprises intracerebral transplantation" (52), "pluripotent cells" having "neuronal and glial potential" (52), and "wherein said transplanted cells migrate and differentiate to replace, or compensate for, said lost or damaged brain cells" (52) are withdrawn because the claims have been canceled.

The metes and bounds of cells "genetically modified to be conditionally immortal" (claim 57) is indefinite because the phrase is not defined in the specification and does not have an art recognized meaning. The structure and genetic modification of cells encompassed by the phrase cannot be determined. The specification states "conditionally immortalized" cells are made by transduction with an oncogene (pg 6, third full para.); however, cells transduced with p53, an oncogene, are not conditionally immortal. The specification teaches the conditions desired in the instant invention required to change the immortality of cells, but does not teach any cells that change immortality as described other than H-2Kb-tsA58. The specification teaches H-2Kb-tsA58 mice were used to make the cells of the instant invention; however, the specification does not describe the vectors used to make H-2Kb-tsA58 mice and Jat (1991), cited on pg 9, line 4, has not been provided and could not be obtained at the time of writing the instant office action. Without such information, it cannot be determined if the claim is limited to cells genetically

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modified to have the tsA58 oncogene or if cells having other oncogenes provide the same "conditional immortality" or are encompassed by the claim.

The phrase "said transplantation" lacks antecedent basis in claim 57. The word following "said" should have literal support in the claim. "Transplanting" does not literally support "transplantation".

The word "but" in claims 57 and 65 is improper because the cells must be immortal prior transplantation and must differentiate after transplantation. Replacing "but" with --and-- is suggested.

The phrase "differentiate to replace, or compensate for, said lost or damaged brain cells" is unclear (claim 58). "Said lost or damaged brain cells" lacks literal support in the claims. It cannot be determined what is required of the cells after being transplanted. Must the cells either differentiate, replace damaged cells or compensate for damaged cells or must the cells differentiate thereby replacing damaged cells or compensating for damaged cells. As written, "to replace..." is an intended use and may or may not occur. If applicants intend the intended use to occur, the function of the cells should be clearly set forth.

The limitation in claim 59 is unclear. While neurons and glial cells can be detected, the moment when cells differentiate into neurons and glial cells cannot be determined. Therefore, it cannot be determined when cells differentiate into neurons or glial cells as claimed. The phrase "in vivo" in claim 59 does not further limit the claim because the cells must differentiate after transplantation in claim 57.

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The metes and bounds of "temperature-sensitive oncogenes" cannot be envisioned (claim 66). The specification does not teach any temperature-sensitive oncogene other than tsA58. The art does not teach any other temperature-sensitive oncogenes. Therefore, it is unclear if "temperature-sensitive oncogene" is limited to tsA58 or if others are included.

Claim Rejections - 35 USC § 102

The rejection of claims 49-56 under 35 U.S.C. 102(b) as being anticipated by Netto (1993, Behavioral Brain Res., Vol. 58, pages 107-112) has been withdrawn because the claims have been canceled.

Claim Rejections - 35 USC § 103

The rejection of claims 49-56 under 35 U.S.C. 103(a) as being unpatentable over Netto (1993, Behavioral Brain Res., Vol. 58, pages 107-112) in view of Bernard (US Patent 5,580,777, 12-3-1996) has been withdrawn because the claims have been canceled.

The rejection of claims 57-67 under 35 U.S.C. 103(a) as being unpatentable over Netto (1993, Behavioral Brain Res., Vol. 58, pages 107-112) in view of Rashid-Doubell (1994, Gene Therapy, Vol. 1, Supp. 1, page S63) has been withdrawn because the claims have been canceled.

4. Claims 57-60, 62 and 65-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Netto (1993, Behavioral Brain Res., Vol. 58, pages 107-112) taken with Renfranz (1991, Cell, Vol. 66, pg 713-729).

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Netto taught transplanting neuroepithelial CA1 cells isolated from hippocampal tissue of day 19-20 embryos into the hippocampus of rats submitted to VO ischemia resulting in hypoxia. The cells caused improved cognitive function in the rats as determined by water maze test. (page 109, column 1, "grafting"; page 108, column 1, "Ischemia"; pg 107, col. line 6; page 108, para, bridging col. 1-2; para. bridging pg 109-110). The cells of Netto are inherently pluripotent. nestin-positive cells as claimed because they were isolated from the same location as described by applicants, caused improved cognitive function as described by applicants, and because applicants do not exclude cells isolated from the hippocampus of mice at day 19-20 from the invention (pg 13, 1st full para.). While the cells used in the examples of the instant invention were isolated from stage 14-15, the patent office does not have the means to test the distinction between cells isolated from the hippocampus of day 14-15 or day 19-20 mouse embryos. Without scientific evidence to the contrary, day 19-20 is similar to day 14-15 in embryo development and day 19-20 is early enough to isolate cells from an embryo that are pluripotent, nestin-positive cells as claimed. Therefore, the cells of Netto are inherently pluripotent, nestinpositive cells. Case law established that reliance upon inherency is not improper even though rejection is based on Section 103 instead of Section 102. In re Skoner, et al. 186 USPQ 80 (CCPA). Netto did not teach the cells were genetically modified.

Renfranz taught a clonal, hippocampal, conditionally immortal, nestin positive, pluripotent, neuroepithelial cell line isolated from E16 rat embryos and transfected with DNA encoding ts SV40 large T antigen (pg 714, "isolation of the HiB5 cell line"). The cell line was

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implanted intracerebrally into 2 day old rats and differentiated (pg 717, "implantation of HiB5 cells into the postnatal cerebellum;" pg 720, "morphological profiles of HiB5 cells in the cerebellum"). Renfranz did not teach administering the cells to a mammal having a cognitive disorder.

It would have been obvious to administer pluripotent, neuroepithelial cells intracerebrally to improve cognitive function as taught by Netto wherein the cells were conditionally immortal as taught by Renfranz. One of ordinary skill in the art at the time the invention was made would have been motivated to conditionally immortalize the cells of Netto to increase the number of cells and to enhance the culture of the cells *in vitro* and to prevent tumor formation upon transplantation (Renfranz, pg 713, col. 2, line 15-22, and last 6 lines of first full para.).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the conditionally immortal, nestin positive, pluripotent, neuroepithelial cell line taught by Renfranz to a mammal having a cognitive disorder as taught by Netto. One of ordinary skill in the art at the time the invention was made would have been motivated to administer the cells of Renfranz to the rat model taught by Netto because the conditionally immortal cells differentiate into multiple phenotypes upon implantation (pg 722, col. 2). One of ordinary skill in the art at the time the invention was made would have been motivated to administer the conditionally immortal cells of Renfranz to a rat having a cognitive disorder to determine whether the conditionally immortal cells are physiologically active *in vivo* as suggested by Renfranz (pg 724, col. 1, line 22-23). One of ordinary skill in the art would have

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had a reasonable expectation of improving the cognitive function of the rat using the conditionally immortal cells of Renfranz because the cells were stable and differentiated *in vivo* as determined by Renfranz.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

To the extent that applicants arguments relate to the new rejection, applicants arguments are addressed as follows:

Applicants argue the CA1 cells isolated from embryonic day 19-20 taught by Netto are not pluripotent as claimed. Applicants argument is not persuasive. While the cells of Netto were isolated at a different time during embryonic development than the cells taught by applicants (day 19-20 vs. day 14-15), the cells of Netto were isolated from the same location at almost the same time as the cells as those described by applicants and restored cognitive function as claimed. The specification states the cells of the invention may be taken on day 14-15, but does not exclude the skilled artisan to take cells on day 19-20. The declaration states CA1 cells isolated from embryonic day 19-20 are "typically mature, differentiated cells and hence not pluripotent or nestin positive" which implies that cells taken on day 14-15 may be pluripotent and nestin-positive because of the word "typically." Without scientific evidence that CA1 cells isolated from day 19-20 as taught by Netto are not pluripotent or nestin-positive, a mere statement that CA1 cells isolated from day 19-20 are "typically" not pluripotent or nestin-positive is not

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adequate to overcome the rejection. Furthermore, the cells of Renfranz are E16 cells which are nestin positive. Therefore, nestin is not exclusively expressed in E14-E15 cells.

5. Claims 57-62 and 65-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Netto (1993, Behavioral Brain Res., Vol. 58, pages 107-112) taken with Renfranz (1991, Cell, Vol. 66, pg 713-729) as applied to claims 57-60, 62 and 65-67 above, in view of Rashid-Doubell (1994, Gene Therapy, Vol. 1, Supp. 1, pg S63) and White (1992, J. Chem. Neuroanatomy, Vol. 5, pg 327-330).

The combined teachings of Netto and Renfranz taught transplanting clonal, neuroepithelial, nestin-positive, conditionally immortalized cells into the hippocampus of rats having a hippocampal lesion caused by hypoxia. See 103 rejection above. The combined teachings of Netto and Renfranz did not teach the cells were cultured in serum-free media.

However, at the time of filing Rashid-Doubell taught making conditionally immortal hippocampal cells for use in *in vivo* studies and cultured the cells in serum-free media (col. 1, "materials and methods").

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to transplant clonal, neuroepithelial, nestin-positive, conditionally immortalized cells into the hippocampus of rats having a cognitive disorder caused by hypoxia, thereby improving the cognitive deficit as taught by the combined teachings of Netto and Renfranz wherein the cells were cultured in serum free media. One of ordinary skill in the art at the time the invention was made would have been motivated to culture the cells in serum-free

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media to improve the differentiation of the cells *in vivo* as taught by White. White taught the presence of >1% serum in culture decreased differentiation of pluripotent neural cells *in vivo* whereas serum-free media increased differentiation of pluripotent neural cells *in vivo* (pg 329, col. 1, first full para.).

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL C. WILSON PATENT EXAMINER